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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,373	12/06/2001	Hans Bigalke	Merz 32 PCT US/dln	4496

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	5

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,373	BIGALKE ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant Preliminary amendment filed December 6, 2001 is acknowledged. The preliminary amendment submitted December 6, 2001 has been entered as follows: Claims 1-6 have been cancelled. Newly submitted claims 7-14 have been renumbered 11-18 respectively, pursuant to 37 CFR 1.126. It should be noted that original claims 7-10 are pending in the instant application. Claims pending and under examination are original claims 7-10 and (newly submitted claims 7-14) which have been renumbered as claims 11-18.

Specification

2. The use of the trademarks have been noted in this application for example on pages 1. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

3. Claims 7 and 10 are objected to for depending from a canceled claim. Correction is required.

Claim Rejections - 35 USC § 101

4. Claims 7-10 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 7-10 provides for the use of botulinum neurotoxins, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

6. Claim 10 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 recites "who/which", it is unclear as to what the applicant is referring?

7. Claim 11 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites "cosmetic condition"; it is unclear as to what the applicant is referring?

8. Claim 11 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites " "Comprising administration of the botulinum toxin", it is unclear as to whom the toxin is administered?

For Art purposes, the phrase "use of" is being viewed as "a method of using" botulinum neurotoxin to treat disorders of the nervous system or for cosmetic purposes, since the phrase "use of" is a non-statutory class of invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 7, 10 and 16-18 are rejected under 35 U.S.C. 102(b) as anticipated by Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102).*

Claims 7, 10 and 16-18 are drawn to a method of using botulinum neurotoxin to treat disorders of the nervous system and the dystonias comprising spasmodic torticollis and blepharospasm, spasticities such as footdrop, hemifacial spasms, migraine, low back pain, cervical spine disorders or hypersalivation.

Goeschel et al teach a method of treating patients that have torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity with injections of botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that among the patients treated were non-responders (patients that did not show improvement nor muscle weakness or atrophy after at least two successive treatments of neurotoxin). Goeschel et al teach that neutralizing antibodies were found in the sera of all non-responders (patients that have developed neutralizing antibodies against botulinum toxin A) (pages 98-99).Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that when patients were exposed to purified botulinum neurotoxin A or botulinum toxin complex the nerve-muscle preparation allowed the discrimination between the sera that contained antibodies against the neurotoxin and those with antibodies against stabilizing proteins like the hemagglutinins which do not contribute to paralysis (page 101). Goeschel et al teach that patients testing positive for non-neutralizing antibodies will continue to benefit from the toxin (page 101). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102). Goeschel et al teach that the amount of antibodies

raised against BOTOX (Botulinum toxin A) is linked to the amount of protein applied (page 101, 2nd column).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

10. Claims 8-9 are rejected under 35 U.S.C. 102 (b) as anticipated by Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99).*

Claims 8-9 are drawn to a method of using botulinum neurotoxins from *Clostridium botulinum* of types A, B, C, D, E, For G or a mixture of two or more of these neurotoxins for cosmetic treatment.

Keen et al teach a method of treating patients that have hyperkinetic facial lines (wrinkles) with injections of botulinum toxin A (see the Abstract and pages 95-97). Keen et al teach that antibodies to botulinum toxin A have been described in patients receiving much larger dosages of botulinum for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of

the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

11. Claims 8-9 are rejected under 35 U.S.C. 102 (b) as anticipated by Shelley et al *(J Am Acad Dermatol. 1998, 28:227-9).*

Claims 8-9 are drawn a method of using botulinum neurotoxins from *Clostridium botulinum* of types A, B, C, D, E, For G or a mixture of two or more of these neurotoxins for cosmetic treatment.

Shelley et al teach a method of treating patients that have hyperhidrosis with botulinum toxin A (page 228). Shelley et al teach that treatment with botulinum toxin A abolished hyperhidrosis one week after treatment (page 228). Shelley et al teach that BOTOX (botulinum toxin A) is a safe and effective treatment for hyperhidrosis (227).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 7-13 and 16-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102* in view of Shelley et al *(J Am Acad Dermatol. 1998, 28:227-9)*.

Claims 7-13 and 16-18 are drawn to a method of using botulinum neurotoxin to treat disorders of the nervous system and the dystonias comprising spasmodic torticollis and blepharospasm, spasticities such as footdrop, hemifacial spasms, migraine, low back pain, cervical spine disorders or hypersalivation.

Goeschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goeschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that when patients were exposed to purified botulinum neurotoxin A or botulinum toxin complex the nerve-muscle preparation allowed the discrimination between the sera that contained antibodies against the neurotoxin and

those with antibodies against stabilizing proteins like the hemagglutinins which do not contribute to paralysis (page 10). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102). Goeschel et al teach that the amount of antibodies raised against BOTOX (Botulinum toxin A) is linked to the amount of protein applied (page 101, 2nd column).

Goeschel et al do not teach hyperhidrosis.

Shelley et al teach a method of treating patients that have hyperhidrosis with botulinum toxin A (page 228). Shelley et al teach that treatment with botulinum toxin A abolished hyperhidrosis one week after treatment (page 228). Shelley et al teach that BOTOX (botulinum toxin A) is a safe and effective treatment for hyperhidrosis (227).

It would be *prima facie* obvious at the time the invention was made to treat patients having hyperhidrosis, wherein the patient exhibits neutralizing antibodies against botulinum toxin A with purified botulinum toxin A because Shelley et al teach that patients treated with botulinum toxin A showed complete abolishment of hyperhidrosis in one week and Goeschel et al teach that purified botulinum neurotoxin preparations (botulinum toxin A) devoid of toxoid and purified from concomitant proteins will reduce the load of foreign substances that might lead to untoward reactions (the development of neutralizing antibodies) (page 102). It would be expected barring evidence to the contrary, that a purified botulinum toxin preparation (free of complexing

proteins) would be effective in treating hyperhidrosis as well as reducing the formation of neutralizing antibodies against the botulinum toxin.

13. Claims 7-12 and 14-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102* in view of Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99).*

Claims 7-12 and 14-18 are drawn to a method of using botulinum neurotoxin to treat disorders of the nervous system and the dystonias comprising spasmodic torticollis and blepharospasm, spasticities such as footdrop, hemifacial spasms, migraine, low back pain, cervical spine disorders or hypersalivation.

Goeschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goeschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that when patients were exposed to purified botulinum neurotoxin A or botulinum toxin complex the nerve-muscle preparation allowed the discrimination between the sera that contained antibodies against the neurotoxin and those with antibodies against stabilizing proteins like the hemagglutinins which do not contribute to paralysis (page 10). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might

lead to untoward reactions (page 102). Goeschel et al teach that the amount of antibodies raised against BOTOX (Botulinum toxin A) is linked to the amount of protein applied (page 101, 2nd column).

Goeschel et al do not teach facial wrinkling.

Keen et al teach a method of treating patients that have hyperkinetic facial lines (wrinkles) with injections of botulinum toxin A (see the Abstract and pages 95-97). Keen et al teach that botulinum toxin A injections eliminated hyperfunctional facial lines (wrinkles) in healthy aesthetic surgical patients (page 94). Keen et al teach that antibodies to botulinum toxin A have been described in patients receiving much larger dosages of botulinum for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient. Keen et al teach that the use of botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in aesthetic surgical patients for a period of 4 to 6 months (page 99).

It would be *prima facie* obvious at the time the invention was made to treat patients having facial wrinkling, wherein the patient exhibits neutralizing antibodies against botulinum toxin A with purified botulinum toxin A because Keen et al teach that the use of botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in aesthetic surgical patients for a period of 4 to 6 months and Goeschel et al teach that the use of purified botulinum neurotoxin preparations (botulinum toxin A) devoid of toxoid and purified from concomitant proteins will reduce the load of foreign substances that might lead to untoward reactions (the development of neutralizing antibodies) (page 102). It would be expected barring evidence to the

contrary, that a purified botulinum toxin preparation (free of complexing proteins) would be effective in eliminating facial wrinkles as well as reducing the formation of neutralizing antibodies against the botulinum toxin.

Status of Claims

14. No claims are allowed.

Pertinent Prior Art

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Benedetto, International Journal of Dermatology, 1999, 28, 641-655).*

Conclusion

16. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
December 16, 2003

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